REMARKS

The Examiner rejected claims 9, 16-17, 19-22, 46, 59-66, 77-80, 85, 87-92, and 95-97. Claims 19-22 have been cancelled without prejudice or disclaimer. Applicants have added no new claims. Claims 9, 16-17, 46, 59-66, 77-80, 85, 87-92, and 95-97 are pending.

Claims 9, 17, 59, 85, 95, and 96 have been amended to more clearly describe the subject matter being claimed. Claim 9 has been amended to delete the language "a mixture of." Claims 17 and 96 have been amended to rephrase the language "protein has a sequence of amino acids at or within about 20 amino acids from the amino terminal end comprising one of SEQ ID NO: 69 or 11" in order to more clearly describe the claimed invention. Claim 59 has been amended to replace the language "PEF protein P45" with the language "SEQ ID NO:71." Claim 85 has been amended to recite "SEQ ID NOS: 72-73" instead of "SEQ ID NOS: 72-81."

Claims 95 and 96 have been amended to replace the language "under stringent conditions" with the language "wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C overnight" in order to more clearly describe the conditions under which a sequence in the claimed invention would hybridize. Support for this amendment may be found, for example, in Example 6, on page 31 of the specification, lines 7-14, and 31-33.

These amendments add no new matter. The changes to the amended claims are shown in the marked up version of the claims in the attached Appendix.

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Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 9, 16, 17, 19, 20, 22, 59, 61, 63, 79, 85, and 95-96 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Office Action, paragraph bridging pages 2-3.

Recitation of "Complex"

The Examiner rejects claims 9, 16, 61, and 63 for recitation of the terms "protein complex" or "PEF complex." Office Action, page 3, paragraph 4. The Examiner alleges that the specification does not define the term "protein complex" or "PEF complex." Further, the Examiner alleges that the term "PEF complex" is indefinite because one could not determine if a "complex" is merely a non-covalent mixture of proteins, or if the elements of the complex are covalently bound to each other. *Id.* Finally, the examiner alleges that it is not clear whether other molecules besides proteins are encompassed by the term "polymerase enhancing factor." *Id.*

Page 6, lines 20-21, of the specification state that "the PEF complexes of the invention comprise protein components and function to enhance the activity of polymerase." The specification at page 6, lines 11-14, further states, as a non-limiting example, that the "PEF complexes of the invention possess polymerase enhancing activity and generally comprise multiple protein subunits with a combined molecular weight of approximately 250 kD or above as determined by SDS-PAGE analysis and gel filtration of unheated PEF samples."

It is well known among those of skill in the art that different subunits of a protein complex can interact in different ways. For example, protein subunits may interact through weak, or secondary (non-covalent) forces, such as ionic or Van der Waals

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forces. Protein subunits may also interact through disulfide bonds between cysteine residues. The term "complex" encompass both those embodiments wherein different protein subunits are covalently attached to one another, and those embodiments where the protein subunits are not covalently attached. One skilled in the art would not consider the term "complex" indefinite in view of such interactions.

It is also well known among those of skill in the art that protein complexes may contain non-protein molecules. For example, human hemoglobin contains four protein subunits and a number of iron molecules. As another example, lipoproteins contain proteins and lipids. PEF complexes are defined in the specification as complexes that comprise more than one protein subunit and enhance the activity of polymerases. *See* the specification, page 6, lines 11-14 and 20-21. One of skill in the art would understand that protein complexes may have molecules other than proteins as part of the complex.

The term "complex" in claims 9, 16, 61, and 63 does not render the claims indefinite under 35 U.S.C. §112, second paragraph.

Recitation of "Synthetic Proteins"

The Examiner rejects claims 9 and 19 as allegedly being indefinite for the recitation of the language "wholly or partially synthetic proteins." Office Action, page 3, paragraph 5.

The Examiner states that the language is unclear absent a statement indicating what the term "synthetic protein" means. However, the Examiner demonstrates that such a statement is unnecessary in the next sentence by stating that "[t]he term 'synthetic' when related to polypeptides is usually associated in the art with chemical

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synthesis of polypeptides from amino acid monomers." *Id.* Thus, not only would the term "synthetic protein" be clear to one of skill in the art, it is apparently clear to the Examiner, also.

Further, the Examiner states that "[i]t is not common in the art to obtain entire proteins by chemical synthesis but rather by recombinant expression in a host cell or by isolating them from their natural sources." *Id.* Thus, the Examiner's contention is that the synthesis of whole proteins is not commonly performed. However, an allegation that a procedure is not common does not support a rejection that a claim is indefinite.

Finally, the Examiner states that it is not clear how a protein can be wholly synthetic. *Id.* The Examiner then makes a statement that it is not clear how a protein can be "partially synthetic." *Id.* It appears that the Examiner is concerned with how to create a wholly or partially synthetic protein. A wholly synthetic protein may be a peptide of any length that is chemically synthesized. A partially synthetic protein may be created by attaching a short synthetic peptide to a purified naturally occurring protein or protein fragment or to a recombinantly produced protein or protein fragment. In fact, the Examiner has suggested the Examiner understands what is meant by a "partially synthetic" protein by stating that such a protein "would require producing part of a protein in a cell and the rest added by chemical synthesis." Office Action, page 3, paragraph 5. Thus, the Applicants respectfully submit that the language "wholly or partially synthetic proteins" satisfies the requirements of 35 U.S.C. §112, second paragraph.

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Recitation of "Mixture of One"

The Examiner rejects claim 9 for recitation of the language "mixture of one." Office Action, page 4, paragraph 7. Without acquiescing to the Examiner's rejection, the language "a mixture of" has been removed from the claim so that claim 9 now recites "comprising [a mixture of] one or more ... ." Thus this rejection is moot.

Recitation of "a protein having a sequence ..."

The Examiner rejects claims 17, 20, and 96 for the recitation of "a protein having a sequence of amino acids at or within about 20 amino acids from the amino terminal end comprising one of SEQ ID NO: 11 or 69." Office Action, page 4, paragraph 8.

Without acquiescing to the rejection, Applicants have amended claims 17 and 96 to recite the language "a protein having a sequence comprising SEQ ID NO: 11 or 69, wherein the sequence comprising SEQ ID NO: 11 or 69 is within about 20 amino acids from the amino terminal end of the protein." Claim 20 has been cancelled without prejudice or disclaimer. Thus the rejection is moot.

Improper Claim Dependency

The Examiner rejects claim 19 because it allegedly depends from a cancelled claim. Office Action, page 4, paragraph 9. Without acquiescing to the rejection, claim 19 has been cancelled. Thus, the rejection is moot.

Recitation of "said component"

The Examiner rejects claim 19 for the recitation of the language "said component." Office Action, page 5, paragraph 10. Without acquiescing to the rejection, claim 19 has been cancelled. Thus, the rejection is moot.

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Recitation of "further comprising a subunit encoded by a DNA having the nucleotide sequence of SEQ ID NO: 70"

The Examiner rejects claim 22 because claim 22 allegedly did not further limit the scope of claim 21, from which claim 22 depended. Office Action, page 5, paragraph 11. Without acquiescing to the rejection, claim 22 has been cancelled. Thus, the rejection is moot.

Recitation of "DNA construct comprising a sequence encoding PEF protein 45"

The Examiner rejects claim 59 because the language is allegedly unclear without a sequence identifier. Office Action, page 5, paragraph 12. Without acquiescing to the rejection, the Applicant has followed the Examiner's suggestion, and claim 59 has been amended to recite the language "encoding SEQ ID NO: 71." Thus, the rejection is moot.

Recitation of "a protein ... comprising one or more of SEQ ID NO: 72-81"

The Examiner rejects claim 85 because the language is allegedly unclear as to how a protein can comprise more than one sequence. Office Action, page 5, paragraph 13. One of skill in the art would understand that more than one given sequence may be found within a protein. Two different peptide sequences can be found within one single chain of amino acids. For example, hypothetical sequence A can be contiguous with hypothetical sequence B, and the resulting protein would comprise both sequences A and B. The word "comprise" is not exclusive - meaning that a protein that "comprises" one sequence may also have other sequences, too.

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The Applicants respectfully submit that claim 85 satisfies the requirements of 35 U.S.C. §112, second paragraph.

Recitation of "under stringent conditions"

The Examiner rejects claims 95-96 because the language is allegedly unclear absent a statement indicating the conditions under which hybridization is performed. Office Action, page 5, paragraph 14. Without acquiescing to the rejection, the Applicant has followed the Examiner's suggestion, and claims 95-96 has been amended to recite the specific hybridization conditions. The claims now recite the language "wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C overnight."

The Applicants respectfully submit that claims 95 and 96 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Applicants respectfully traverse the §112, second paragraph, rejections, and requests reconsideration and withdrawal of them.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 9, 16, 19, 64, 80, and 87-92 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Office Action, pages 6-12.

The Examiner rejects claims 9, 19, and 80 as allegedly not being enabled because, the Examiner asserts that the specification does not provide enablement for all analogs of P45. *Id.*, page 6, section 16. More specifically, the Examiner asserts that the specification does not enable one of skill in the art to predict the sequence of all analogs of P45 that would possess polymerase enhancing activity. *Id.*, page 7-8,

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section 16. The Examiner states that in would require undue experimentation to determine all analogs of P45 that possess activity. *Id.*

The Applicants respectfully assert that the Examiner is applying the enablement test incorrectly. As long as the specification discloses at least one method of making the invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. Manual of Patent Examining Procedure (MPEP) § 2164.01 (b). "Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112." *Id.*

It would not require one of skill in the art an undue amount of experimentation to determine whether any single given analog of P45 possessed polymerase enhancing activity. A screening assay for polymerase enhancing acitivity is described in the specification in Example 1, pages 20-22.

In *In Re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the court reversed a finding of lack of enablement under §112, first paragraph. *See* MPEP §2164.06(b), under "Several Decisions Ruling That The Disclosure Was Enabling." The nature of the invention in that case involved the generation of monoclonal antibodies, and then screening the monoclonal hybridomas to determine which monoclonals possessed the desired characteristics. Although one of skill in the art could not predict the structure of all antibodies that would fit the claimed invention in that case, the court found that the specification was sufficient to allow one of skill in the art to determine which antibodies possessed the desired characteristics, and thus fell within the scope of the claims. Thus, the specification in *In Re Wands* was found to be enabling for monoclonal antibodies, the structure of which were not necessarily predictable.

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Similarly, the specification in this case enables one of skill in the art to determine whether a given protein possesses polymerase enhancing activity. Such an assay does not represent undue experimentation. The specification need not enable one to predict the exact structure of all analogs that possess polymerase enhancing activity, but need only enable one of skill in the art to determine whether an analog possesses polymerase enhancing activity. The specification in this case is sufficiently enabling for claims 9, 19, and 80 under 35 U.S.C. § 112, first paragraph.

The Examiner rejects claim 16 as allegedly not being enabled because the Examiner asserts that the specification is not enabling for any polymerase enhancing protein with a molecular weight of 17-18 kD from *P. furiosus*. Office Action, pages 8-9, section 18. Specifically, the Examiner asserts that one could not accurately predict which *P. furiosus* proteins of 17-18 kD would enhance polymerase activity. *Id.*

As the Applicants respectfully point out above, the Examiner has again stated the enablement test incorrectly. For the reasons asserted above, without undue experimentation, one of skill in the art would be able to test any *P. furiosus* protein of 17-18 kD to determine whether it enhanced polymerase activity. The enablement requirement does not require that the specification describe or predict every single structure that falls within the scope of the claims. A screening assay for polymerase enhancing acitivity is described in the specification in Example 1, pages 20-22. It is sufficient that the specification enable one of skill in the art to determine whether any given 17-18 kD protein of *P. furiosus* possesses polymerase enhancing activity. Claim 16 is sufficiently enabled by the specification under 35 U.S.C. § 112, first paragraph.

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The Examiner rejects claim 64 as allegedly not being enabled because the Examiner asserts that the specification is not enabling for a fusion protein with P45. Office Action, pages 10-11, section 19. Specifically, the Examiner asserts that the specification does not indicate which proteins could be fused with P45. *Id.*

Once again, the Examiner mistakenly believes that §112, first paragraph, requires that the specification describe or predict all embodiments of the claimed invention. The enablement requirement does not require that the specification describe or predict every single structure that falls within the scope of the claims. A screening assay for polymerase enhancing activity is described in the specification in Example 1, pages 20-22. It is sufficient that the specification enable one of skill in the art to determine whether any given P45 fusion protein possesses polymerase enhancing activity. As the Examiner points out, the creation of fusion proteins is known to those of skill in the art, including the creation of fusion proteins that do not affect the original function of the protein (such as those created for the purposes of purification). Office Action, page 10, third paragraph.

The Examiner has failed to establish that amount of experimentation required to generate fusion proteins and screen them with the assay disclosed in the specification does rises to the level of undue experimentation. Applicants respectfully submit that claim 64 is sufficiently enabled by the specification under 35 U.S.C. § 112, first paragraph.

The Examiner rejects claims 87-92 because the Examiner asserts that the specification does not enable any *T. thermophilis* protein with dUTPase activity that enhances polymerase activity. Office Action, pages 11-12, section 20. Specifically, the

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Examiner asserts that the specification does not provide any examples of polymerase enhancing *T. thermophilis* dUTPases, or provide any information on critical structural elements.

The specification need not contain a working example if the claimed invention is otherwise disclosed in a manner that one of skill in the art could practice the invention without undue experimentation. MPEP §2164.01(c). In this case, a screening assay for polymerase enhancing activity is described in the specification in Example 1, pages 20-22. It would require no undue experimentation for one of skill in the art to determine if a *T. thermophilis* dUTPase enhanced polymerase activity by using the assay disclosed in the specification.

Further, it is not required that the specification describe exactly how an invention works in order to be enabling. Disclosure of the critical structural elements of either the P45 protein or a *T. thermophilis* dUTPase is not required to demonstrate enablement under the *In Re Wands* factors.

The disclosed assay provides a sufficient way to determine if a *T. thermophilis* dUTPase enhances polymerase activity without any undue experimentation. Claims 87-92 are enabled under 35 U.S.C. §112, first paragraph.

Applicants respectfully traverse the §112, first paragraph, rejections, and requests reconsideration and withdrawal of them.

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Rejections Under 35 U.S.C. § 102

The Examiner rejects claim 85 under 35 U.S.C. §102(a) as allegedly being anticipated by Bult, et al., PIR accession number F64353, and Bult et al., PIR accession

number E64437 (collectively "Bult"). Office Action, page 13, section 21. Specifically, the Examiner alleges that Bult discloses SEQ ID NOS: 74 and 75. *Id.*

The Examiner also rejects claim 85 under 35 U.S.C. §102(b) as allegedly being anticipated by Kletzin, Wang et al., Lundberg et al., Gadsden et al., Mercer et al., and Albrecht et al. Office Action, pages 13-14, section 22. Specifically, the Examiner alleges that Kletzin, Wang et al., Lundberg et al., Gadsden et al., Mercer et al., and Albrecht et al. disclose SEQ ID NOS: 76, 77, 78, 79, 80, and 81 respectively. *Id.*

Without acquiescing to the rejections, claim 85 has been amended to recite "SEQ ID NO: 72-73." Thus, claim 85 as amended is not anticipated by Bult, Kletzin, Wang et al., Lundberg et al., Gadsden et al., Mercer et al., and Albrecht et al.. Accordingly, and the §102 rejections are moot.

Applicants respectfully traverse the §102 rejections and requests reconsideration and withdrawal of them.

Rejection for Double Patenting

The Examiner rejects all claims as allegedly being unpatentable over claims of U.S. Patent No. 6,183,997, to Hogrefe ("Hogrefe") under the nonstatutory judicially created doctrine of obviousness-type double patenting. Office Action, pages 14-15, sections 23 and 24.

Without acquiescing to the rejection, if the claims are otherwise found in condition for allowance, the Applicants will file a terminal disclaimer.

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Conclusion

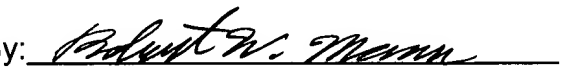
The application is in condition for allowance. Applicants request the timely allowance of the application. In the event the Examiner does not find the claims allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6676 to set up an interview.

Please grant any extensions of time required to enter this Amendment and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 29, 2002

By: 

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APPENDIX

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9. (Twice Amended) A non-naturally occurring composition of matter comprising a protein complex possessing nucleic acid polymerase enhancing activity, the complex comprising a plurality of subunits wherein at least one subunit has a molecular weight of approximately 17-18 kD in the fully denatured, monomeric form, and wherein the complex is selected from the group consisting of: a polymerase-enhancing protein complex of one or more wholly or partially synthetic proteins having the same amino acid sequence as the naturally-occurring protein or analogs thereof possessing polymerase enhancing activity; or a polymerase-enhancing protein complex comprising [a mixture of] one or more of the naturally occurring or wholly or partially synthetic proteins.

17. (Thrice Amended) A composition of matter according to claim 16, wherein said protein is selected from the group consisting of: a protein having a sequence [of amino acids at or within about 20 amino acids from the amino terminal end] comprising [one of] SEQ ID NO: 69 or 11[;], wherein the sequence comprising SEQ ID NO: 11 or 69 is within about 20 amino acids from the amino terminal end of the protein; a protein encoded by a nucleic acid having the sequence of SEQ ID NO: 70 or a sequence that hybridizes to the complement of the nucleotide sequence of SEQ ID NO: 70 under stringent conditions; or a protein having a sequence of amino acids comprising SEQ ID NO:71.

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59. (Twice Amended) A P45 protein produced from a cell containing a DNA construct comprising a sequence encoding SEQ ID NO: 71 [PEF protein P45] operably linked to an expression vector, wherein the protein is in monomeric, dimeric, or multimeric form.

85. (Amended) A protein having PEF activity comprising one or more of SEQ ID NO: 72-73 [81].

95. (Twice Amended) A non-naturally occurring composition of matter comprising a polymerase-enhancing protein encoded by a DNA sequence that hybridizes to the complement of the nucleotide sequence of SEQ ID NO: 70 [under stringent conditions], wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C overnight.

96. (Twice Amended) A non-naturally occurring composition of matter comprising a polymerase-enhancing protein encoded by a DNA sequence that hybridizes [under stringent conditions] to the complement of a nucleotide sequence that encodes a protein, wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C overnight; and wherein said protein has a sequence [of amino acids at or within about 20 amino acids from the amino terminal end] comprising [one of] SEQ

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ID NO: 69 or 11[;], wherein the sequence comprising SEQ ID NO: 11 or 69 is within about 20 amino acids from the amino terminal end of the protein.

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